Patent Claims

Claim 1

An irrigation system for medical care comprising

(a) a plurality of pressurisable reservoirs containing prescribed irrigation fluid;

(b) fluid conduction means for leading the said fluid through selectively from the said reservoir to a first prescribed position;

(c) a first pressure source to control pressure in a first reservoir which is one of the said reservoirs, by communicating through to the said reservoir;

(d) a second pressure source to control pressure in a second reservoir which is one of the said reservoirs, by communicating through to the said reservoir;

(e) a regulation means, which in cooperation with the first and second pressure source, pressurizes the first and second pressurisable reservoirs independently;

to selectively and correspondingly pressurize the fluid in said reservoirs.

Claim 2

An irrigation system for medical care of Claim 1 characterised in that the aforesaid pressurisable reservoir is enclosed.

Claim 3

An irrigation system for medical care of Claim 1 characterised in that the aforesaid first and second reservoirs are not connected and are separate.

Claim 4

An irrigation system for medical care of Claim 1 characterised in that the aforesaid first and second pressure source are connected to single pressure pump.

Claim 5

An irrigation system for medical care of Claim 1 characterised in that the fluid in the said first reservoir is identical to the fluid in the said second reservoir.

Claim 6

An irrigation system for medical care of Claim 1 characterised in that the aforesaid fluids from the said reservoirs are simultaneously lead through to the first prescribed position.

Claim 7

An irrigation system for medical care of Claim 1 characterised in that the aforesaid fluids from the said reservoirs are sequentially lead through to the first prescribed position.

Claim 8

An irrigation system for medical care of Claim 1 characterised in that the said regulation means includes a regulation panel containing a display that indicates the pressure in each reservoir.

Claim 9

An irrigation system for medical care of Claim 1 characterised in that it further includes, in combination, a self-contained power supply which supplies activation power from battery.

Claim 10

An irrigation system for medical care comprising

(a) a plurality of enclosed flexible reservoirs containing prescribed liquid for medical care;

(b) fluid conduction means for leading the said fluid through selectively from the said reservoirs to a first prescribed position;

(c) a first air bladder to control pressure in a first reservoir which is one of the said reservoirs, by communicating as a pressure through to the said reservoir;

(d) a second air bladder to control pressure in a second reservoir which is one of the said reservoirs, by communicating as a pressure to the said reservoir;

(e) a means connected to the first and second air bladders, in order to pressurize the first and second air bladders independently;

to selectively and correspondingly pressurize the said fluid.

Claim 11

An irrigation system for medical care of Claim 10 characterised in that furthermore, a pair of pressure pump valves are included which are individually mutually connected with the said first and second air bladders, to have the effect that when they are activated so that the pressure should be released from said air bladders selectively, independently and rapidly.

Claim 12

An irrigation system for medical care of Claim 10 characterised in that

(a) alarm means; and

(b) the pressure detection means which responds to accidental pressure release of one of said reservoirs, in order to activate said alarm means;
are also provided.

Claim 13

An irrigation system for medical care of Claim 10 characterised in that means to provide and maintain a fixed pressure in said reservoirs is also included.

Claim 14

An irrigation system for medical care of Claim 11 characterised in that
(a) alarm means; and
(b) the pressure detection means which responds to accidental pressure release of one of said reservoirs, in order to activate said alarm means;
are also provided.

Claim 15

An irrigation system for medical care of Claim 12 characterised in that means to provide and maintain a fixed pressure in said reservoirs is also included.

Claim 16

An irrigation system for medical care of Claim 12 characterised in that it also includes means which, in order to activate said alarm means, respond to accidental cessation of flow of liquid for medical care.

Claim 17

An irrigation system for medical care characterised in that it provides
(a) a plurality of enclosed flexible reservoirs containing prescribed liquid for medical care;
(b) fluid conduction means for leading the said liquid for medical care through selectively from the said reservoirs to a first prescribed position;
(c) a first air bladder to control pressure in a first reservoir which is one of the said reservoirs, by communicating through to the said reservoir in a pressure conduction state;
(d) a first pressure release means connected to the said first air bladder, to release the pressure from the said first air bladder rapidly;
(e) a second air bladder to control pressure in a second reservoir which is one of the said reservoirs, by communicating through to the said reservoir in a pressure communicating state;

(f) a second pressure release means connected to the said second air bladder, to release the pressure from the said second air bladder rapidly;
(g) means connected to said first and second air bladders which standardly pressurizes said first and second air bladders in order to selectively and correspondingly pressurize said liquids;
(h) means to provide and maintain a fixed pressure in each reservoir;
(i) alarm means; and
(j) the pressure detection means which responds to accidental pressure release inside one of said reservoirs, in order to activate said alarm means;
(k) fluid detection means which, in order to activate said alarm means, respond to accidental cessation of flow of liquid for medical care.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely, irrigation system for medical care, particularly a continuously controllable system for the flow of irrigation liquid from a plurality of reservoirs.

(0002)

Technology of the Prior Art

In the medical field, there are cases in which irrigation of wound, amputation or other physical opening is required or is highly desirable, but many problems arise. Often, the required quantity of irrigation fluid exceeds the volume of conventionally used fluid source, such as 1-litre container or the like. Moreover, it is often necessary or highly desirable to maintain irrigation state without altering the flow rate of fluid.

(0003)

In past, moreover, in order to achieve a continuous uninterrupted flow of the fluid, it has been proposed to expand the effective reservoir by providing piping from a common or central fluid source and the like. However, this causes other problems such as limitation of the kind of irrigation that can be used, or increase of vulnerability with respect to contamination. In the state in which the total amount of fluid is small, it can be executed just by regulating with respect to the container which supplies such small amounts. Example of such regulation which supplies for non-irrigation is disclosed in US Patent 4,657,160 specification published April 14, 1987 by Andy Woods and Peter Giannini. In the said specification, a pressure infusion system is disclosed in which a flexible bag

containing a fixed quantity of liquid to be infused is enclosed by a pressure band for forcibly forwarding the liquid from the said bag. However, when contents of flexible bag were exhausted, the bag needs to be replaced with a separate bag, and accordingly a temporary interruption of flow is caused. Accordingly, a system suitable for use with a plurality of fluid sources, providing the selectable flow that is continuously controlled is still required.

(0004)

Problems to be Overcome by this Invention

The object of this invention is to improve irrigation system for medical care.

(0005)

Another object of this invention is to put forward continuous flow of irrigation fluid from a plurality of reservoirs.

(0006)

Another object of this invention is to promote the use of irrigation fluids from a plurality of reservoirs.

(0007)

A further object of this invention is to promote the use and adjustment of irrigation fluid controller.

(0008)

Another object of this invention is to produce a fluid controller simply, and to reduce the cost.

(0009)

Means to Overcome these Problems

In accordance with this invention, (a) a plurality of pressurisable reservoirs containing a prescribed irrigation fluid; (b) fluid conduction means for leading the said fluid through selectively from the said reservoir to a first prescribed position;

(c) a first pressure source to control pressure in a first reservoir which is one of the said reservoirs, by communicating through to the said reservoir;

(d) a second pressure source to control pressure in a second reservoir which is one of the said reservoirs, by communicating through to the said reservoir;

(e) a regulation means, which in cooperation with the first and second pressure source, pressurizes the first and second pressurisable reservoirs independently; is provided, to selectively and correspondingly pressurize the fluid in said reservoirs.

(0010)

In accordance with this invention, it may be manipulated so as to selectively and controllably pressurise a plurality of liquid reservoirs individually, and in this way, by developing an improved control system, in which the fluid flow can be continuously controlled even when the liquid reservoir is refilled or replaced, and a continuous flow of fluid from a plurality of reservoirs is given.

(0011)

Moreover, it may be provided with pressure and flow rate alarm, pressure indicator and quick pressure open valve.

(0012)

Accordingly, one distinctive feature of this invention is to provide an easily controllable pressure source at low price for individually pressurising a plurality of separate, flexible-walled pressurisable reservoirs which are respectively fitted with pressure bands in a physically linked condition.

(0013)

A separate distinctive feature of this invention, is to put forward a simple system wherein a common pressure source is used, having air as the source.

(0014)

Yet another separate distinctive feature of this invention, is that a pair of fluid flow and pressure vent (a dump) controllers are established on each pressure reservoir, which impart simple regulation of individual fluid flow, rapid switching and/or emergency cut-off.

(0015)

Moreover, a separate distinctive feature of this invention, is to equip with device for establishing and maintaining a specified pressure level and/or fluid flow rate in a separate embodiment, which contributes to the efficiency of the apparatus.

(0016)

Yet another separate distinctive feature of this invention in a separate embodiment, is to equip with device for detection and control via the use of a sensor.

(0017)

Preferred form for carrying out the invention.

Hereinafter, this invention will be described in further detail while referring to attached figures, however, this invention is not restricted to these.

(0018)

Referring to Figure 1, a general system illustrating basic system elements is shown. Wherein, the power supply which may be conventionally used alternating current power supply 11 or battery 12 is connected to air pump 14 through conventionally used electrical switch 13. Air pump 14 is pneumatically connected through conventionally used tubing 15 to air header 16. Thereafter, air header 16 is connected to air bladder compression assembly body 17a-17d through header extension parts 16a-16d. As will be understood by those skilled in the art, components 11-16 are conventional off-the-shelf components and are readily available through a variety of commercial suppliers.

(0019)

In other words, as shown in Figure 1, the air bladder compression assembly bodies (for example 17a-17d) are each comprised of a pressure bladder, namely a pressurised band 18 in engagement with a flexible irrigation fluid bag 19. When the pressure bladder is inflated, the pressure is communicated to the said flexible irrigation fluid bag 19. Wherein, according to preferred embodiment, the pressure bladders of the air bladder compression assembly bodies 17a-17d are similar to conventional blood pressure band which are generally available from a variety of commercial sources.

(0020)

As described earlier, Figure 3 is a more detailed diagram illustrating a battery powered embodiment of the preferred system according to the invention. It shows that conventional alternating current source 11 is connected to conventional battery charge circuits 20, in accordance with principles well known in the art, and operating electric power is maintained on battery 12. The conduction from battery charge and battery supply circuit is a serially interposed circuit protective device such as a circuit breaker or fuse 21 or the like. From these circuits, conduction is made via path 23 to "push-to-set" pressure level switch 24 and via lead 25 to relay 26. There, it is seen to be connected via path 27 to provide power to several system components as shown in the illustration.

(0021)

Relay 26 is connected via path 28 so as to be under the control of Run Power/Alarm switch assembly 29. Thus, Run Power/Alarm switch assembly 29 acts as a master switch that is used to start and stop system operation. When it is desired to activate the system, a conventional electrical switch S1 in assembly body 29 is actuated to operate relay 26 and to begin system operation.

(0022)

It should be noted that path 23 provides power for switch 24 irrespective of whether or not power switch S1 in switch assembly is on or off, thus providing for activation of conventional display logic 30 so that it may be set for the desired pressure level which is advantageous for the production of air pressure by pump 14. Provision is also made for energization of 3-digit conventional pressure display so that it is powered up and ready to display pressure as soon as main power switch S1 (module 29) is turned on. Moreover, a desired pressure level may be set through conventional pressure level selector 32.

(0023)

It will be observed from reference to Internal Power Distribution Circuit 33 that when relay 26 is closed, provision is made for producing three levels of direct current voltage: (1) +2.5 Volts; (2) +4.1 Volts; and (3) –3 Volts which are represented respectively by arrows 34, 35 and 36. These are applied to various ones of the remaining circuit modules as identified by correspondingly numbered inputs. Thus, turning on of main power switch S1 and closing of relay 26 provides energy at the different voltage levels needed to operate the system.

(0024)

By the way, referring to "Push-to-Set" pressure level switch 24 (the type which switch is pushed, and is set pressure level), it will be seen that it is connected via path 37 to pressure level selector 32. Thus, when it is desired to set the desired level of air pressure in air header 16, a conventional push button in switch module 24 is depressed and the desired level of pressure is selected by manipulation of conventional Pressure Level Selector 32. As the level is being selected, its value is displayed through logic 30 and display 31. When the selected level is accepted by the operator, its value is communicated via path 38 to pressure logic module 40 whence it is effective via path 41 to condition pump control module 42 which in turn is effective via path 43 to control conventional pump 14.

(0025)

Since noise reduction is particularly important in medical environments, provision is made for muffling the sound of air as it enters the pump intake. This is accomplished by muffler which is shown connected to pump 14 by input manifold 45.

(0026)

Returning to Pressure Logic 40, it will be seen that it is additionally controlled by Pressure Detection Circuit Module 46 which is connected to air header 16 via paths 47 and 48. Thus, when the pressure in header 16 is less than the selected value, module 46 communicates to the pressure logic 40 via path 49, thus resulting in pump control 42 to correspondingly condition pump 14.

(0027)

In order to provide for safe operation of the equipment, an over pressure limit switch 50 is provided to sense air header pressure via path 47. If such pressure rises to a predetermined level, then pump control 42 is overridden via path 51 and the pump is instantaneously shut down. At the same time, an alarm signal is conducted via path 52 to visual alarm circuit 53 where it activates a visual alarm and sends a signal via path 54 to activate audio alarm circuit 55 and optional buzzer 56.

(0028)

In addition, an additional level of alarm and control is represented by paths 57 and 58 which interconnect Pressure Logic module 40 with Visual Alarm Circuit module 53 and Pressure Detection Circuit module 46.

(0029)

With further reference to Figure 3, pump air outflow vessel 60 which connects pump 14 to reservoir 61 and conventionally used check valve 62 are found. Air is introduced into vessel 47 through vessel 63 at said check valve 62, and thereafter, it is communicated to air header 16. Thereafter, air header 16 is connected to preferably four outputs 64a-64d, which are in turn connected to four air bladders such as air bladders 17a-17d (Figures 1 and 4) directly or preferably through an air management manifold such as manifold 70 (Figure 4).

(0030)

Provision is optionally but preferably made for inclusion of battery monitoring and display circuits. These are conventional and are represented by items 12a and 12b. Inclusion of a battery condition display on the system display panel adds to the usefulness and dependability of the equipment.

(0031)

By the way, referring to Figure 4, Air Management Manifold 70 which is a module of air paths, valves and connectors is schematically shown. Air input to the manifold is represented by path 47 which in turn is connected to a header corresponding to header 16 (Figures 1 and 3) and including branches 16a-16c connected through T's and an elbow 71a-71d. Extending from these T's and elbows are individual air paths 72a-72d which include serially interposed air valves represented by switch elbows 73a-73d, thus providing for individual control of air passing through paths 72a-72d.

(0032)

From the downstream side of air valve 73a-73d, individual air vessel 74a-74d each leads to separate air bladder compression assembly body 17a-17d. Each of said air bladder compression assembly body 17a-17d includes air pressure bladder, namely a pressure band such as symbol 18 or the like of Figure 2 and flexible fluid bag such as 19 or the like of Figure 2. However, when comparing Figure 1 and Figure 2, there is provided, in Figure 4, a series of individual pressure dump valves 75a-75d, the upstream portions 76a-76d of which are in communication with air in pressure bladders 18a-18d (Figure 2); and the downstream portions 77a-77d being directed to any suitable air dump environment. Generally, the air dump environment is the location in which the equipment is used. However, in certain circumstances it may be desired to vent the air dump to some predetermined location, when a hose or other path may be connected to the air dump terminals.

(0033)

The aforesaid air dump valve 75a-75d is operated by manual operation, and/or may be controlled electrically by using the like of connection to the pressure logic circuits 40 of Figure 3. Well known various kinds of valve can be used.

(0034)

It will now be evident to those skilled in the art that there has been described herein an improved automatic pump and air ballast squeeze system that provides a number of features including provision for individual control of a plurality of flexible bags together

with fluid flow control, ability to change bags without fluid flow interruption, and over/under pressure alarm or shut-down.

(0035)

Wherein, this invention with respect to preferred embodiment was described, it will be evident that other adaptations and modifications can be employed without departing from the spirit and scope thereof. For example, alternatives may be employed for the squeeze bag assemblies.

(0036)

Wherein, the terms and expressions employed herein have been used as terms of description and not of limitation. Accordingly, there is no intent of excluding equivalents, but on the contrary it is intended to cover any and all equivalents that may be employed without departing from the spirit and scope of the invention.

Brief Description of the Figures

Figure 1

Figure 1 is a block diagram illustrating a general system according to the principles of the invention.

Figure 2

Figure 2 is a block diagram illustrating the paired relationship of pressure bladders and flexible fluid bags in accordance with the invention.

Figure 3

Figure 3 a more detailed diagram illustrating the preferred system according to the invention.

Figure 4

Figure 4 is a block diagram illustrating an air management manifold according to the invention.

Key to Symbols

11: alternating current power supply

12: battery

14: air pump

61: reservoir

17a-17d : air bladder compression assembly body,

Figure 1

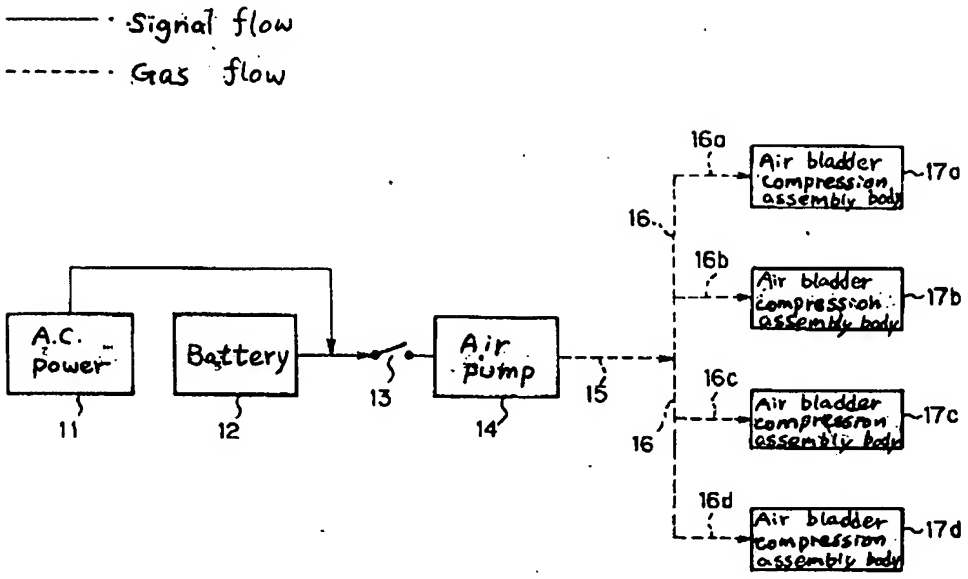


Figure 2

17a-d

Pressure bladder	Flexible fluid bag
18a-18d	19a-19d

Figure 3

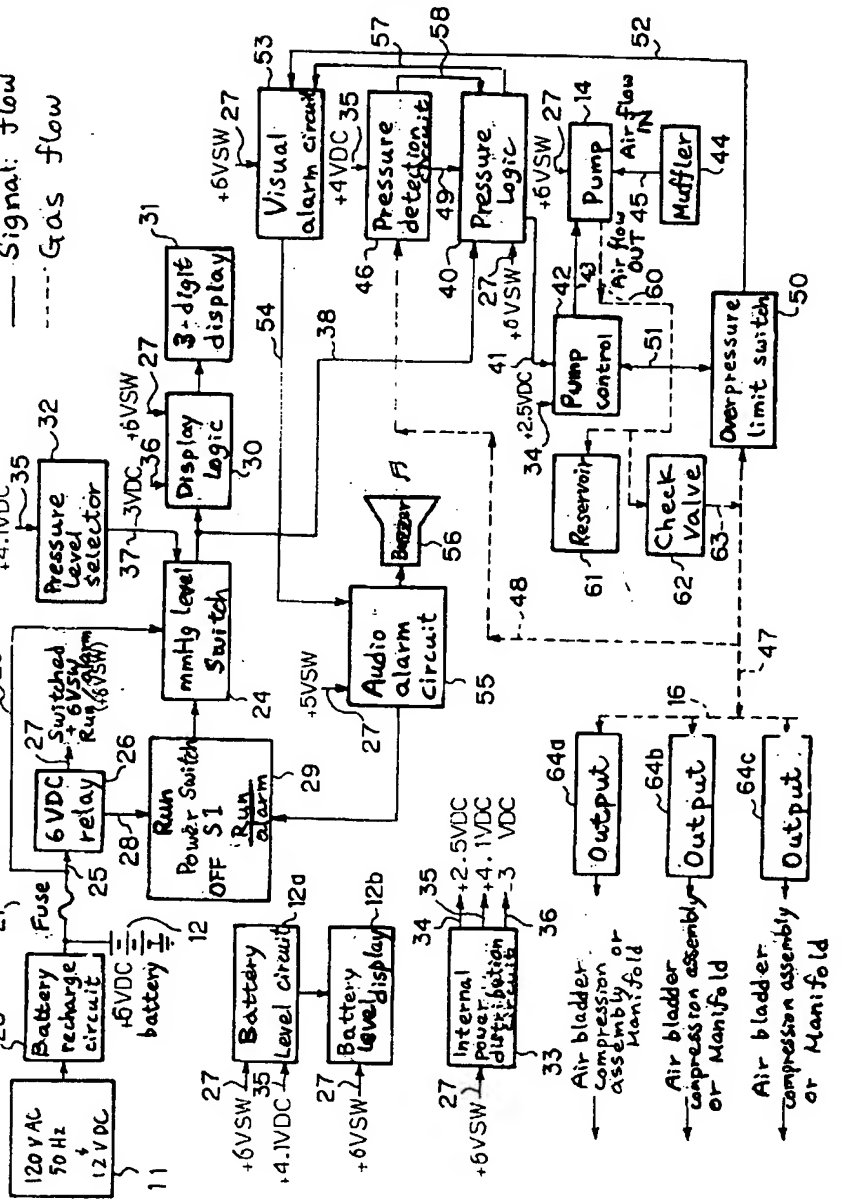
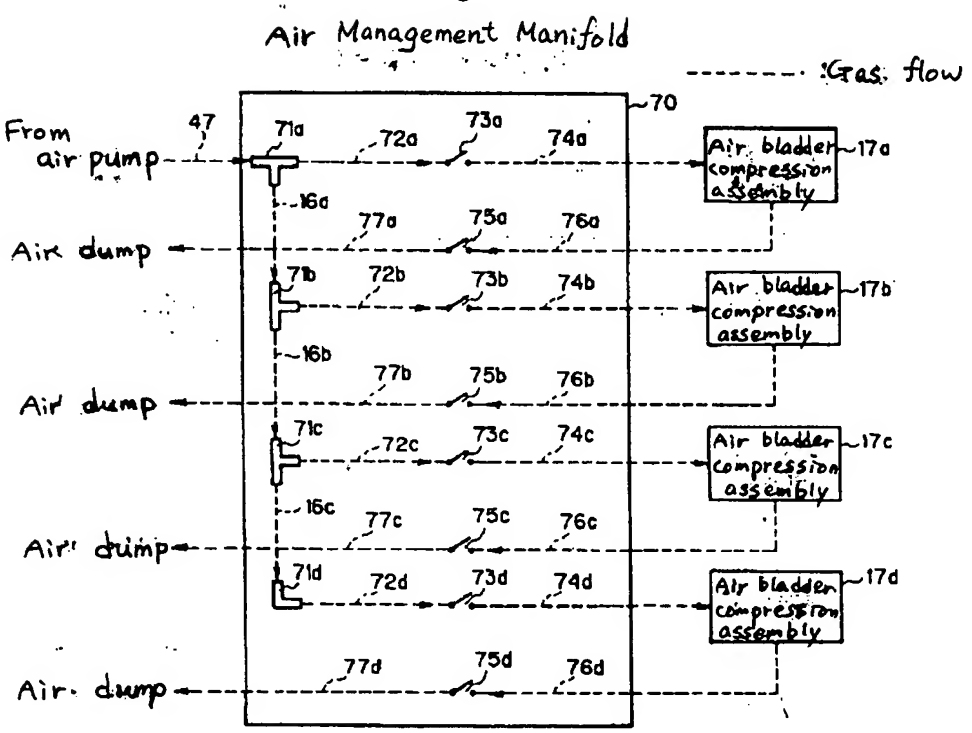

— Signal flow
---- Gas flow
120 VAC 50 Hz → 12 VDC
Battery recharge circuit
Fuse
+6VDC battery
6 VDC relay
Switched +6VSW Run (6VSW)
Run Power Switch S1 OFF
Run alarm
Battery Level circuit
Battery Level display
Internal power distribution circuit
+2.5VDC
+4.1VDC
-3 VDC
mmHg level Switch
Pressure Level selector
+4.1VDC
3-digit display
Display Logic
+3VDC
+6VSW
Audio alarm circuit
+5VSW
Buzzer
Visual alarm circuit
Pressure detection circuit
+4VDC
Pressure Logic
Pump
Air flow IN
Muffler
Air flow OUT
Pump control
+2.5VDC
Overpressure limit switch
Reservoir
Check Valve
Output
Air bladder compression assembly or Manifold

Figure 4


Air Management Manifold
Gas flow
From air pump
47
70
71a
72a
73a
74a
Air bladder compression assembly
17a
16a
77a
75a
76a
Air dump
71b
72b
73b
74b
Air bladder compression assembly
17b
16b
77b
75b
76b
Air dump
71c
72c
73c
74c
Air bladder compression assembly
17c
16c
77c
75c
76c
Air dump
71d
72d
73d
74d
Air bladder compression assembly
17d
77d
75d
76d
Air dump

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)
Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

Rising Sun Communications Ltd. retains the copyright to all of its' translation products unless expressly agreed in writing to the contrary. The original buyer is permitted to reproduce copies of a translation for their own corporate use at the site of purchase, however publication in written or electronic format for resale or other dissemination to a wider audience is strictly forbidden unless by prior written agreement.

The Full Terms and Conditions of Business of Rising Sun Communications may be found at the web site address <http://www.risingsun.co.uk/Terms_of_business.html>

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（A）**　(11)特許出願公開番号

特開平8－173525

(43)公開日　平成８年(1996)７月９日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｍ　1/00	５００			
Ｆ０４Ｂ　49/06	３２１			

審査請求　未請求　請求項の数17　ＯＬ　（全 ８ 頁）

(21)出願番号　特願平7－221748

(22)出願日　平成７年(1995)８月30日

(31)優先権主張番号　２９９４２８

(32)優先日　1994年９月１日

(33)優先権主張国　米国（ＵＳ）

(71)出願人　595124859
リーランド・エル・ラド
Ｌｅｌａｎｄ　Ｌ．　Ｌａｄｄ
アメリカ合衆国フロリダ州34698，ダニディン，マッカーティー　1080

(72)発明者　リーランド・エル・ラド
アメリカ合衆国フロリダ州34698，ダニディン，マッカーティー　1080

(74)代理人　弁理士　湯浅　恭三　（外６名）

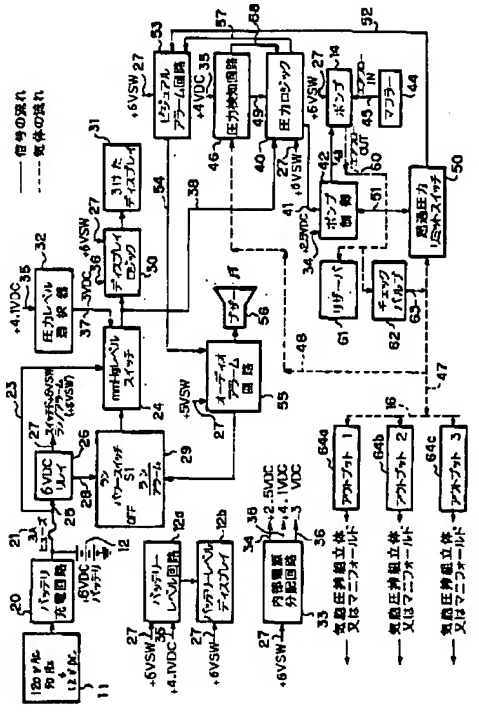
最終頁に続く

(54)【発明の名称】　医療用灌注ポンプ及びシステム

(57)【要約】

【課題】　複数のリザーバから灌注流体の連続流を提供する医療用灌注システムを改良する。

【手段】　所定の灌注流体を含有する複数の加圧可能なリザーバ６１、該リザーバから第１の位置まで該流体を選択的に導通させる導通手段、第１のリザーバと連通して圧力を制御するための第１の圧力源、第２のリザーバと連通して圧力を制御するための第２の圧力源、第１及び第２の圧力源と共働して、加圧可能な第１及び第２のリザーバを独立的に加圧する制御手段を備える。



1

【特許請求の範囲】

【請求項1】（a）所定の灌注流体を含有する複数の加圧可能なリザーバ；

（b）該リザーバから第1の所定の位置まで該流体を選択的に導通させるための流体導通手段；

（c）該リザーバのうちの一つである第1のリザーバと連通して、該第1のリザーバ内の圧力を制御するための第1の圧力源；

（d）該リザーバのうちの一つである第2のリザーバと連通して、該第2のリザーバ内の圧力を制御するための第2の圧力源；

（e）該第1及び第2の圧力源と協働して、該第1及び第2の加圧可能なリザーバを独立的に加圧する制御手段を備え、該リザーバ内の流体を選択的且つ対応的に加圧することを特徴とする医療用灌注システム。

【請求項2】　前記加圧可能なリザーバが囲包されていることを特徴とする請求項1の医療用灌注システム。

【請求項3】　前記第1及び第2のリザーバが不連続で、分離していることを特徴とする請求項1の医療用灌注システム。

【請求項4】　前記第1及び第2の圧力源が、単一の圧力ポンプに連結されていることを特徴とする請求項1の医療用灌注システム。

【請求項5】　前記第1のリザーバ中の流体が、前記第2のリザーバ中の流体と同一であることを特徴とする請求項1の医療用灌注システム。

【請求項6】　前記リザーバからの流体が、前記第1の所定の位置まで同時に導通されることを特徴とする請求項1の医療用灌注システム。

【請求項7】　前記リザーバからの流体が、前記第1の所定の位置まで連続的に導通されることを特徴とする請求項1の医療用灌注システム。

【請求項8】　前記制御手段が、各リザーバ内の圧力を表示するディスプレイを有する制御パネルを含むことを特徴とする請求項1の医療用灌注システム。

【請求項9】　さらに、バッテリーからの賦活力を供給する自己収納型電源を組合せとして含むことを特徴とする請求項1の医療用灌注システム。

【請求項10】　（a）所定の医療用液体を含有する囲包された複数の可撓性リザーバ；

（b）該リザーバから第1の所定の位置まで該医療用液体を選択的に導通させるための流体導通手段；

（c）該リザーバのうちのひとつである第1のリザーバと圧力連通し、該第1のリザーバの圧力を制御するための第1の気胞；

（d）該リザーバのうちのひとつである第2のリザーバと圧力連通し、該第2のリザーバの圧力を制御するための第2の気胞；

（e）該第1及び第2の気胞を独立的に加圧するため、該第1及び第2の気胞に連結されている手段を備え、該

2

液体を選択的且つ対応的に加圧することを特徴とする医療用灌注システム。

【請求項11】　さらに、前記第1及び第2の気泡と個別的に相互連結された一対の圧力ポンプバルブを含み、選択的、独立的及び迅速的に該気胞から圧力を解放するべく賦活されたときに、有効となることを特徴とする請求項10の医療用灌注システム。

【請求項12】　（a）アラーム手段；

（b）該アラーム手段を賦活するため、前記リザーバの一つの偶発的な圧力の解放に対して応答的な圧力検知手段をさらに備えることを特徴とする請求項10の医療用灌注システム。

【請求項13】　さらに、前記リザーバ内の圧力を一定に設定し且つ維持するための手段を含むことを特徴とする請求項10の医療用灌注システム。

【請求項14】　（a）アラーム手段

（b）該アラーム手段を賦活するため、前記リザーバの一つの偶発的な圧力の解放に対して応答的な圧力検知手段をさらに備えることを特徴とする請求項11の医療用灌注システム。

【請求項15】　さらに、前記リザーバ内の圧力を一定に設定し且つ維持するための手段を含むことを特徴とする請求項12の医療用灌注システム。

【請求項16】　さらに、前記アラーム手段を賦活するため、医療用液体の流れの偶発的な停止に応答する手段を含むことを特徴とする請求項12の医療用灌注システム。

【請求項17】　（a）所定の医療用液体を含有する囲包された複数の可撓性リザーバ；

（b）該リザーバから第1の所定の位置まで該医療用液体を選択的に導通させるための流体導通手段；

（c）該リザーバのうちのひとつである第1のリザーバと圧力連通状態にあり、該第1のリザーバ内の圧力を制御するための第1の気胞；

（d）該第1の気胞に連結されており、該第1の気胞から圧力を迅速に解放するための第1の圧力解放手段；

（e）該リザーバのうちのひとつである第2のリザーバと圧力連通状態にあり、該第2のリザーバ内の圧力を制御するための第2の気胞；

（f）該第2の気胞に連結されており、該第2の気胞から圧力を迅速に解放するための第2の圧力解放手段

（g）該第1及び第2の気胞に連結され、該第1及び第2の気胞を標準的に加圧して、選択的且つ対応的に該液体を加圧するための手段；

（h）各リザーバ内での圧力を選択的に設定し且つ一定に維持するための手段；

（i）アラーム手段；

（j）該アラーム手段を賦活するため、該リザーバの一つ内の圧力の偶発的な解放に応答する圧力検知手段；

（k）該アラーム手段を賦活するため、液体流の偶発的

な停止に応答する液体流検知手段を備えることを特徴とする医療用灌注システム。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、医療用灌注システムに関し、特に複数のリザーバからの灌注流体の流れを連続制御可能なシステムに関する。

【０００２】

【従来の技術】医療の現場では、創傷、切断あるいは他の身体の開口の灌注が必要であるか若しくは所望される場合に、多数の問題が生じている。しばしば、灌注流体の所要量は、１リットル容器等の慣用の流体源の容量を越えてしまう。さらに、流体の流速を変えることなく、灌注状態を維持することが必要であり若しくは所望されることが多い。

【０００３】過去において、また連続的で途切れない流体の流れを達成するために、共通若しくは中央の流体源からの配管を設けることによる等、効果的なリザーバを拡大することが提案されている。しかしながら、これは、利用可能な灌注の種類を概して制限してしまい、あるいは汚染物質に対する脆弱性を増加させる等の別の問題を引き起こしている。流体の総量が少ない状態では、かような少量を供給する容器に対する制御を与えることだけで実行できる。非灌注目的のために供給される流体のかような制御の例は、１９８７年４月１４日付けにて、Andy Woods及びPeter Giannini に発行された米国特許第４，６５７，１６０号明細書に開示されている。該明細書には、注入されるべき一定量の流体を含有する可撓性バッグが、該バッグから液体を強制的に進めるための加圧帯で包囲されている圧力注入システムが開示されている。しかしながら、可撓性バッグの内容物が消尽された場合には、バッグを別のバッグで取り変える必要があり、よって流れの一時的な中断を引き起こす。したがって、複数の流体源の利用に適し、連続的に制御された選択可能な流れを提供することができるシステムがいまだに要求されている。

【０００４】

【発明が解決しようとする課題】本発明の目的は、医療用灌注システムを改良することにある。

【０００５】本発明の別の目的は、複数のリザーバから灌注流体の連続流を提供することにある。

【０００６】本発明の他の目的は、複数のリザーバからの灌注流体の利用を促進することにある。

【０００７】本発明のさらに別の目的は、灌注流体制御装置の使用及び調節を促進することにある。

【０００８】本発明の他の目的は、流体制御装置を簡単に製造することとコストを削減することにある。

【０００９】

【課題を解決するための手段】本発明によれば、（ａ）所定の灌注流体を含有する複数の加圧可能なリザーバ；

（ｂ）該リザーバから第１の所定の位置まで該流体を選択的に導通させるための流体導通手段；（ｃ）該リザーバのうちの一つである第１のリザーバと連通して、該第１のリザーバ内の圧力を制御するための第１の圧力源；（ｄ）該リザーバのうちの一つである第２のリザーバと連通して、該第２のリザーバ内の圧力を制御するための第２の圧力源；（ｅ）該第１及び第２の圧力源と協働して、該第１及び第２の加圧可能なリザーバを独立的に加圧する制御手段を備え、該リザーバ内の流体を選択的且つ対応的に加圧することを特徴とする医療用灌注システムが提供される。

【００１０】本発明によれば、複数の液体リザーバを個々に、選択的に及び制御可能に加圧するように操縦されてもよく、こうして液体リザーバが再充填若しくは置換された場合にも連続制御された液体流を可能とする、改良された制御システムの展開を通して、複数のリザーバからの流体の連続流が与えられる。

【００１１】さらに、圧力及び流速アラーム、圧力インジケータ、及び迅速な圧力開放バルブを備えてもよい。

【００１２】したがって、本発明の特徴の一つとして、複数の分離した可撓性壁の加圧可能なリザーバが、物理的に係合した状態の加圧帯とそれぞれフィットされ、リザーバを個々に加圧するための廉価で容易に制御可能な圧力源を提供する。

【００１３】本発明の別の特徴において、共通の圧力源が用いられ、空気を源とする簡易なシステムが提供される。

【００１４】さらに本発明の別の特徴において、一対の流体流及び圧力ベント（ダンプ）制御器が、各圧力リザーバに設けられ、流体流の簡易な個々の制御、迅速な切り替え、及び／又は緊急の切断を与える。

【００１５】また本発明の別の特徴において、別の実施態様において、所定の圧力レベル及び／又は流体流速の確立及び維持のための装備がなされ、装置の効率に寄与する。

【００１６】さらに本発明の別の特徴において、また別の実施態様において、センサの利用を通して検出及び制御のための装備がなされる。

【００１７】

【好ましい実施の形態】以下、添付図面を参照しながら、本発明をさらに詳細に説明するが、本発明はこれらに限定されるものではない。

【００１８】図１を参照すれば、基本システム要素を示す一般的なシステムが示されている。ここで、慣用の交流電源１１又はバッテリ１２であってもよい電源は、慣用の電気スイッチ１３を介してエアポンプ１４に連結されている。エアポンプ１４は、慣用の管１５を介してエアヘッダー１６に含気的に連結されている。次いで、エアヘッダー１６はヘッダー延長部１６ａ～１６ｄを介して気胞圧搾組立体１７ａ～１７ｄに連結される。当業者

に理解されるように、要素１１～１６は、慣用の既製の要素でよく、商業的に容易に入手可能である。

【００１９】図１に示すように、気胞圧搾組立体（例えば、１７ａ～１７ｄ）は、それぞれ、可撓性灌注流体バッグ１９と係合している圧力胞すなわち加圧帯１８である。該可撓性灌注流体バッグ１９には、圧力胞が膨張したとき、圧力が連通される。ここで、好ましい実施態様に従って、気胞圧搾組立体１７ａ～１７ｄの圧力胞は、種々の市販源から一般に入手可能な慣用の血圧加圧帯と同様のものである。

【００２０】上述したように、図３は、本発明に従う好ましいシステムのバッテリーで賦活された好ましい実施態様を説明するより詳細なダイアグラムである。公知の原理に従いバッテリー１２上に運転電化を維持する慣用のバッテリー充電回路２０に連結された慣用の交流電源１１が示されている。バッテリー充電及びバッテリー供給回路からの導通は、ブレーカ又はヒューズ２１等の直列的に挿入された回路保護装置である。これらの回路から、パス２３を介して「プッシュートゥーセット」(push-to-set)圧力レベルスイッチ２４まで、及びリード２５を介してリレイ２６まで導通する。図示されている幾つかのシステム要素に電力を与えるため、パス２７を介して連結されているように見える。

【００２１】リレイ２６は、ランパワー／アラーム(Run Power/Alarm)スイッチアセンブリ２９により制御されるべきものとして、パス２８を介して連結されている。よって、ランパワー／アラームスイッチアセンブリ２９は、システムのスタート／ストップ操作に用いられるべきマスタースイッチとして作用する。システムを賦活したいときには、組立体２９内の慣用の電気スイッチＳ１が、リレイ２６を操作しシステム操作を開始するように賦活される。

【００２２】パス２３は、スイッチアセンブリにおけるパワースイッチＳ１がｏｎ若しくはｏｆｆのいずれにあっても関係なく、スイッチ２４のためのパワーを与え、よって、慣用のディスプレイロジック３０を賦活させ、ポンプ１４による気圧生成に有利な所望の圧力レベルにセットすることに注意されたい。３桁の慣用の圧力ディスプレイの賦活化をも与え、メインパワースイッチＳ１（モジュール２９）がｏｎされるとすぐに、圧力を表示するためにパワーアップされて準備される。さらに、慣用の圧力レベル選択器３２を介して、所望の圧力レベルをセットしてもよい。

【００２３】内部電源分配回路(Internal Power Distribution Circuit)３３を参照することにより、リレイ２６が閉鎖されるときに、矢印３４、３５及び３６で表される直流電圧の３レベル、すなわち（１）＋２．５ボルト（２）＋４．１ボルト（３）－３ボルトが発生することが明らかであろう。これらは、対応する符号によって示されているインプットとして、残りの回路モジュール

の種々のものに、適用される。よって、メインパワースイッチＳ１をｏｎして、リレイ２６を閉鎖することによって、システムを操作するために必要とされる異なる電圧レベルのエネルギーを与える。

【００２４】さて「プッシュートゥーセット」(push-to-set)圧力レベルスイッチ２４（スイッチを押して圧力レベルをセットするタイプ）を参照すれば、パス３７を介して、圧力レベル選択器３２に連結されていることがわかる。よって、エアヘッダー１６内の気圧を所望のレベルにセットしたいときには、スイッチモジュール２４内の慣用のプッシュボタンを押し下げて、慣用の圧力レベル選択器３２の操作によって、圧力の所望レベルを選択する。レベルが選択されると、ロジック３０及びディスプレイ３１を通して、その値が表示される。選択されたレベルがオペレータによって受け入れられると、その値は、パス３８を介して圧力ロジックモジュール４０まで連通され、ここで、パス４１を介して有効となりポンプ制御モジュール４２を条件設定し、次いで、パス４３を介して有効となり慣用のポンプ１４を制御する。

【００２５】医療環境においては、ノイズの減少が特に重要であるので、気体がポンプ入り口に入る際の音を消音することが必要となる。これは、インプットマニフォールド４５によりポンプ１４に連結されて示されているマフラーにより達成される。

【００２６】圧力ロジック４０に戻れば、パス４７及び４８を介してエアヘッダー１６に連結されている圧力検知回路モジュール４６によって、圧力ロジック４０は追加的に制御されることがわかる。よって、、ヘッダー１６内の圧力が選択された値よりも低い場合には、モジュール４６がパス４９を介して圧力ロジック４０に連通し、結果的にポンプ制御４２によってポンプ１４を対応的に条件設定させる。

【００２７】設備の安全操作のために、超過圧力リミットスイッチ５０を設けて、パス４７を介してエアヘッダー圧力を検知する。かような圧力が所定のレベルまで上昇したならば、ポンプ制御４２はパス５１を越えて、ポンプは瞬間的に停止する。同時に、アラーム信号がパス５２を介して、ビジュアルアラーム回路５３まで導通される。ビジュアルアラーム回路５３は、ビジュアルアラームを活性化させて、信号をパス５４を介して送信して、オーディオアラーム回路５５及び任意的なブザー５６を活性化させる。

【００２８】加えて、アラーム及び制御の追加のレベルが、圧力ロジックモジュール４０とビジュアルアラーム回路モジュール５３及び圧力検知回路モジュール４６とを相互連結させるパス５７及び５８に現れる。

【００２９】さらに図３を参照すれば、ポンプ１４をリザーバ６１及び慣用のチェックバルブ６２に連結するポンプエアアウトフロー導管６０が見られる。該チェックバルブ６２にてエアは導管６３を介して導管４７に導入

され、次いでエアヘッダー１６に連通される。エアヘッダー１６は、次いで、好ましくは４つのアウトプット６４ａ～６４ｄに連結される。次いで、４つのアウトプットは、直接又は好ましくはマニフォールド７０（図４）等のエア管理マニフォールドを通して、気胞１７ａ～１７ｄ等（図１及び図４）の４つの気胞に連結される。

【００３０】備え付けることは任意的であるが、バッテリーモニタリング及びディスプレイ回路を含むことが好ましい。これらは慣用のものでよく、符号１２ａ及び１２ｄで表される。システムディスプレイパネルにバッテリー状態ディスプレイを設けることは、設備の有用性及び独立性を高める。

【００３１】さて、図４を参照すれば、エア導管、エアバルブ及びエアコネクタのモジュールであるエア管理マニフォールド(Air Management Manifold)７０が概略的に示されている。マニフォールドへのエアインプットは、導管４７で示され、該導管４７は、Ｔ字継手及びひじ継手７１ａ～７１ｄを通して連結されているブランチ１６ａ～１６ｃを含むヘッダー１６（図１及び図３）に連結されている。これらのＴ字継手及びひじ継手から延びているのは、独立したエア導管７２ａ～７２ｄである。該エア導管７２ａ～７２ｄは、スイッチひじ継手７３ａ～７３ｄで表される直列的に挿入されたエアバルブを含むので、導管７２ａ～７２ｄを通過するエアは独立的に制御される。

【００３２】エアバルブ７３ａ～７３ｄの下流側からは、個々のエア導管７４ａ～７４ｄがそれぞれ分離した別々の気胞圧搾組立体１７ａ～１７ｄまで導く。該気胞圧搾組立体１７ａ～１７ｄのそれぞれは、図２の符号１８等の気圧胞すなわち加圧帯と図２の符号１９等の可撓性流体バッグとを含む。しかしながら、図１及び図２と対比すれば、図４においては個々の圧力ダンプバルブ７５ａ～７５ｄ、圧力胞１８ａ～１８ｄ（図２）内のエアと連通する上流部分７６ａ～７６ｄ、及び適当なエアダンプ環境に向けられた下流部分７７ａ～７７ｄがある。一般的に、エアダンプ環境は、設備が使用される位置にある。しかしながら、ある状況においては、ホース又は他の導管がエアダンプターミナルに連結されるような場合、ある所定の位置にエアダンプを排気することが望ましい。

【００３３】前述のエアダンプバルブ７５ａ～７５ｄは、手動によって操作されても及び／又は図３の圧力ロジック回路４０への連結等により電気的に制御されてもよい。公知の種々のバルブを用いることもできる。

【００３４】当業者にとって、複数の可撓性バッグの個々の制御と共に流体流れ制御、流体流れに影響を与えない該バッグの取り替え、及び圧力が超過／不足の際のアラーム又は回路切断等を含む多くの特徴を提供する改良された自動ポンプ及びエアバラスト圧搾システムが記載されていることが明らかであろう。

【００３５】ここでは、好ましい実施態様について本発明を記載したが、本発明の範囲を逸脱しない限りにおいて他の適応及び変更がなされてもよい。例えば、圧搾バッグ組立体の代わりに別のものが用いられてもよい。

【００３６】ここで用いられている語彙及び説明は、記載を明らかにするために用いられているものであって、本発明をなんら限定するものではない。よって、等価と見られるものを除外するものではなく、本発明の範囲から逸脱しない限りにおいて、すべての等価なものを用いることができる。

【図面の簡単な説明】

【図１】図１は、本発明の原理に従ってなされた一般的なシステムを示すブロックダイアグラムである。

【図２】図２は、本発明に従ってなされた圧力胞及び可撓性流体バッグの間の対にされた関係を示すブロックダイアグラムである。

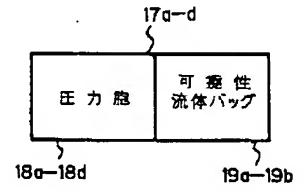
【図３】図３は、本発明による好ましいシステムをより詳細に示すダイアグラムである。

【図４】図４は、本発明によるエア管理マニフォールドを示すブロックダイアグラムである。

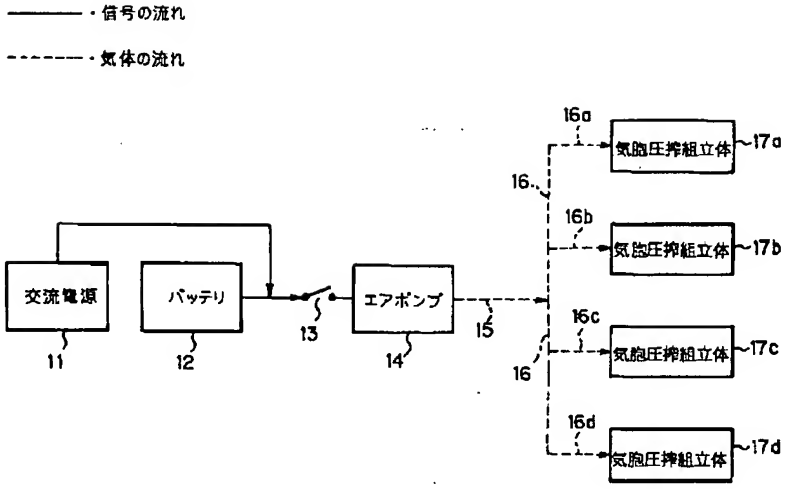
【符号の説明】

１１：交流電源
１２：バッテリー
１４：エアポンプ
６１：リザーバ
１７ａ～１７ｄ：気胞圧搾組立体

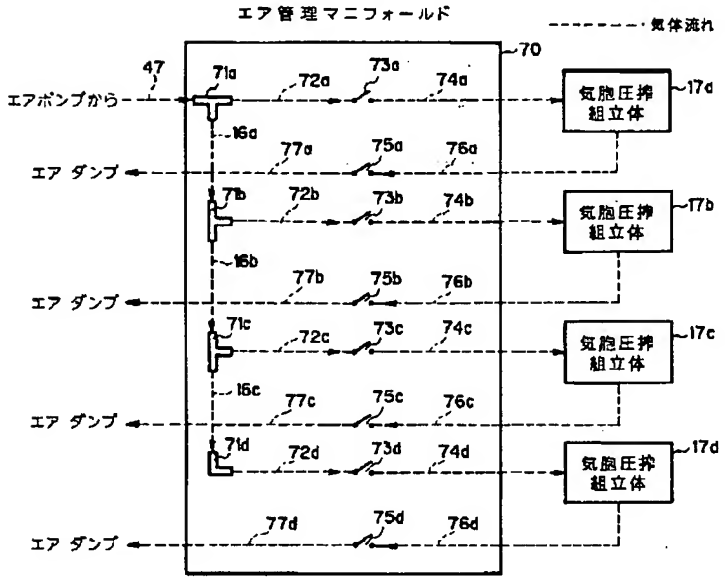
【図２】



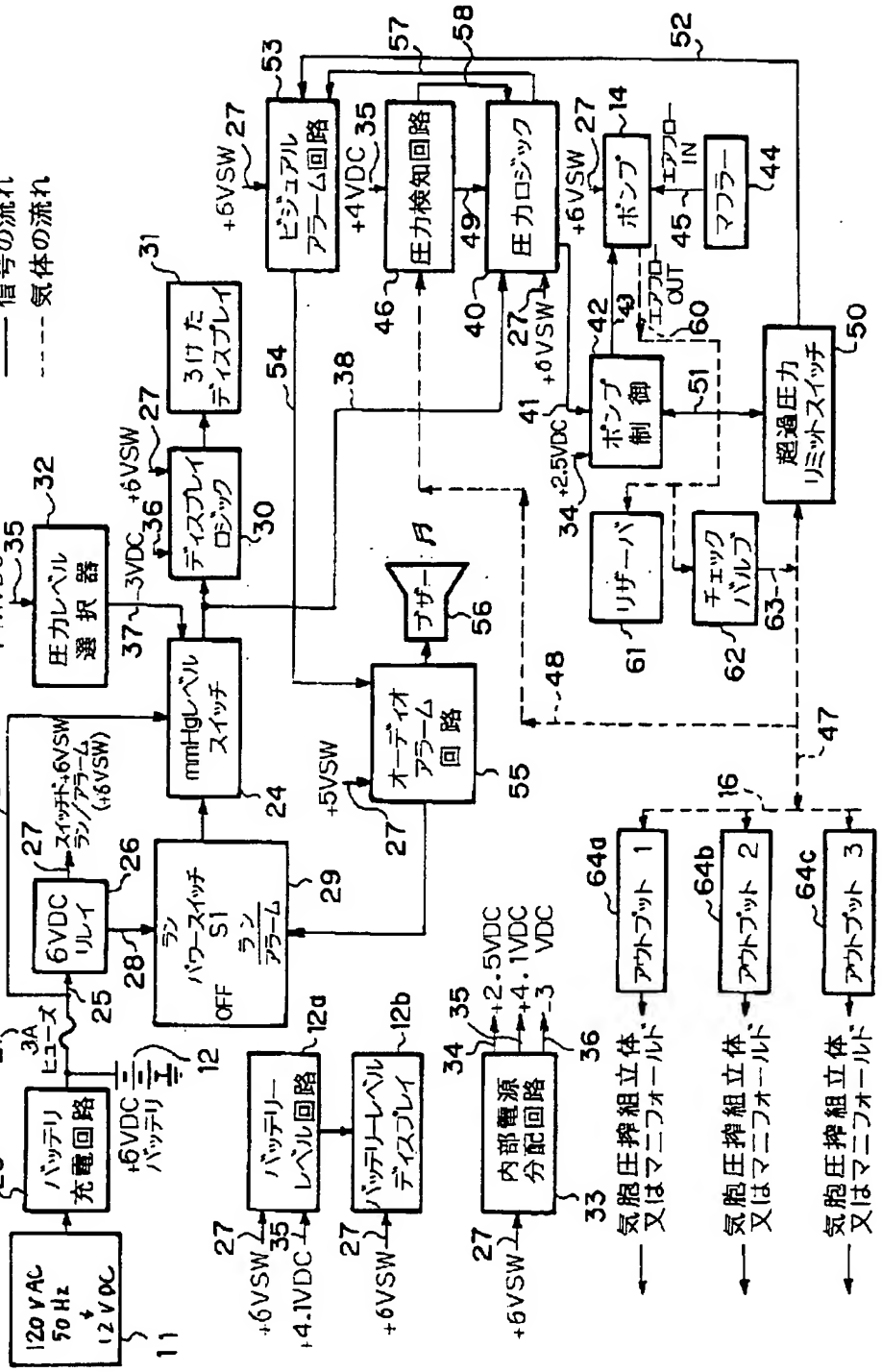
【図1】


信号の流れ
気体の流れ
交流電源
バッテリ
エアポンプ
11
12
13
14
15
16
16a
16b
16c
16d
気胞圧搾組立体
17a
17b
17c
17d

【図4】


エア管理マニフォールド
気体流れ
70
47
エアポンプから
エア ダンプ
71a
72a
73a
74a
75a
76a
77a
71b
72b
73b
74b
75b
76b
77b
71c
72c
73c
74c
75c
76c
77c
71d
72d
73d
74d
75d
76d
77d
16a
16b
16c
気胞圧搾組立体
17a
17b
17c
17d

【図3】


信号の流れ
気体の流れ
120VAC 50Hz → 12VDC
充電回路
バッテリ
ヒューズ 3A
6VDC バッテリ
バッテリーレベル回路
バッテリーレベルディスプレイ
内部電源分配回路
+2.5VDC
+4.1VDC
VDC
6VDC リレイ
スイッチ+6VSW ランプ/アラーム (+6VSW)
ラン パワースイッチ S1 OFF
ラン アラーム
mmHgレベル スイッチ
圧力レベル選択器
+4.1VDC
3VDC
ディスプレイ ロジック
+6VSW
3けた ディスプレイ
ビジュアル アラーム回路
+5VSW
オーディオ アラーム回路
ブザー
圧力検知回路
+4VDC
圧力ロジック
ポンプ制御
+2.5VDC
ポンプ
エアフロー IN
エアフロー OUT
マフラー
超過圧力 リミットスイッチ
リザーバ
チェック バルブ
アウトプット 1
アウトプット 2
アウトプット 3
気胞圧搾組立体 又はマニフォールド
気胞圧搾組立体 又はマニフォールド
気胞圧搾組立体 又はマニフォールド

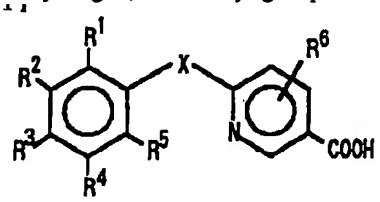
フロントページの続き

(71)出願人　595124859
1080 McCarty, Dunedin, Florida 34698, United States of America

(57) (Abstract)

(Construction)

A topical agent containing a compound represented by the following formula (wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group and the like, and X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group and the like)



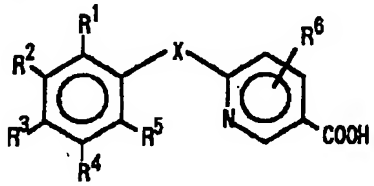
(effect)

It has excellent skin deterioration prevention action, and is stable with small percutaneous absorption, safety is high. Moreover, because it is readily metabolised, side effects due to retinoid action is small.

Patent Claims

[Claim 1]

A topical agent containing a compound represented by the following formula:



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

[Claim 2]

A topical agent in accordance with Claim 1, having skin deterioration prevention action.

[Claim 3]

A topical agent in accordance with Claim 1, wherein aforesaid compound is a compound that is not substantially absorbed percutaneously.

[Claim 4]

A topical agent in accordance with the Claim 1, wherein the local and/or systemic cytotoxicity is reduced.

[Claim 5]

A skin deterioration inhibitor for topical use, containing a compound in accordance with Claim 1 as effective ingredient.

(Detailed Description of the Invention)

(0001)

(Sphere of Application in Industry)

This invention is related to a topical agent, in particular, a topical agent having skin deterioration prevention action.

(0002)

(Technology of the Prior Art)

In order to prevent skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging, various topical agents have been used. In such topical agents, a component that protects the skin from the external factor such as sun, a component that acts on the skin itself and promotes activation of skin, and the like are formulated. As an effective ingredient having the latter action, Vitamin A or derivatives thereof are attracting attention.

(0003)

It is known that the retinoic acid which is an active metabolite of vitamin A (vitamin A acid) binds to a specific receptor of the target cell, and physiological effect is displayed, and the compound which binds to this receptor (retinoid receptor) and displays retinoic acid-like action is generally known generally as retinoid. Moreover, it is known that retinoid has various kinds of actions such as vision control action, growth stimulation action, reproduction action and the like, and in particular it plays an important function for the normal differentiation and maintenance of skin. In some cases, topical agent containing vitamin A and some retinoids may be topically used for the purpose of skin deterioration prevention. However, in practice, whether a rough skin, dryness, follicular hyperkeratosis and the like are inhibited by retinoid or not, or whether the effective for skin deterioration prevention or not, is not known.

(0004)

On the other hand, the retinoids sometimes used for aforesaid purpose, in general have a highly lipid soluble characteristics, and when applied as a topical agent, they are quickly absorbed to the body from the skin (percutaneous absorption), and there is a situation that systemic side effect such as hyperretinoidosis and the like are accompanied in addition to the target topical action (skin deterioration prevention action). Moreover, these retinoids were not readily decomposed locally and in vivo, and there was case that side effect due to cell injury is induced, and there are many restrictions for the application for the purpose of skin deterioration prevention.

(0005)

On the other hand, as compound having retinoid action, benzoic acid derivatives in accordance with Kokai 61-22047, Kokai 61-76440 are known. Moreover, pyridine carboxylic acid derivatives having retinoid action are disclosed in Kokai 6-263702, EP Laid-Open 617020-A1 and PCT WO93/6086. As for pyridine carboxylic acid derivatives disclosed in Kokai 6-263702 EP Laid-Open 617020-A1, usefulness as anti bone disease medicine is known as well (Kokai 7-17854), however, it has not been suggested or indicated in any of these publications that these derivatives have skin deterioration prevention action.

(0006)

As for the pyridine carboxylic acid derivatives disclosed in PCT WO93/6086, it is indicated in said publication that it is useful for therapy of dermatosis, however, there is no suggestion nor indication that these derivatives have skin deterioration prevention action. Moreover, these pyridine carboxylic acids have 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro naphthyl group or 3-adamantyl phenyl group, and has an extreme lipid soluble characteristic.

(Problems to be Overcome by this Invention)

The object of this invention is to put forward a topical agent which has excellent skin deterioration prevention action. In a further embodiment, the object of this invention is to put forward aforesaid topical agent, wherein a compound having retinoic acid action is contained as effective ingredient, and cytotoxicity is reduced. Moreover, another object of this invention is to put forward a topical agent having excellent skin deterioration prevention action which has no systemic side effect such as hyperretinoidosis.

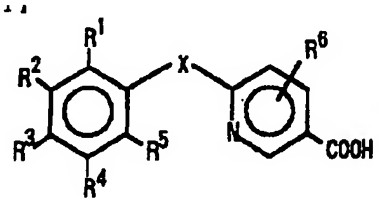
(0007)

(Means to Overcome these Problems)

These inventors carried out assiduous investigations in order to solve aforesaid problem, as a result, discovered that nicotinic acid derivatives of the following formula having activity of retinoic acid had extremely excellent skin deterioration prevention action. Moreover, these inventors also discovered that these compounds were comparatively hydrophilic, had little percutaneous absorption properties, and also were readily decomposed on skin and in vivo, therefore systemic cytotoxicity was remarkably reduced. This invention was completed on the basis of aforesaid findings.

(0008)

In other words, this invention puts forward a topical agent containing a compound represented by the following formula:



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

(0009)

In accordance with the preferred form of aforesaid invention, aforesaid topical agent having skin deterioration prevention action, aforesaid topical agent wherein, aforesaid compound is a compound which is not substantially absorbed percutaneously, and aforesaid topical agent wherein topical and/or systemic cytotoxicity is reduced, are put forward. Moreover, in accordance with another form of this invention, a skin deterioration inhibitor for topical use containing aforesaid compound as effective ingredient is put forward.

(0010)

In aforesaid compound contained in topical agent of this invention, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, either of straight chain or branched alkyl group may be used, and as further example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert butyl group, n-pentyl group, iso pentyl group, neopentyl group, n-hexyl group and the like can be used. Among these, ethyl group, isopropyl group or tert butyl group is preferably used. As C1-6 alkoxy group, either of straight or branched chain alkoxy group may be used, and as a

further example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert butoxy group and the like can be used. As halogen atom, any of fluorine atom, chlorine atom, bromine atom or iodine atom may be used.

(0011)
For example, among such compounds, a compound in which two adjacent or non-adjacent substituents selected from the aforesaid R1, R2, R3, R4 and R5 are same or different alkyl groups is a preferred compound as the component of topical agent of this invention. For example, a compound in which R2 and R3, or R2 and R4 are both alkyl groups is preferred. Among such compounds, the compound wherein the alkyl group is ethyl group, isopropyl group or tert butyl group is more preferred, and methylene group is particularly preferred.

(0012)
R6 denotes hydrogen atom, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, halogen atom or C1-6 alkoxy group, aforesaid species can be used. R6 can be substituted at arbitrary position of 2-position, 5-position or 6-position of pyridine ring. Among these the compound in which R6 is hydrogen atom is preferred.

(0013)
In more concrete terms, as component of topical agent of this invention, compounds such as 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-t-butylphenyl carbamoyl) nicotinic acid or 6-(3,5-di-t-butylphenyl carboxamide) nicotinic acid and the like are preferred, but the component of topical agent of this invention is not restricted to these preferred compounds. Moreover, in topical agent of this invention, one or more of aforesaid compounds can be used in a combination thereof. Moreover, arbitrary base addition salt and arbitrary hydrate of aforesaid compound may be used. For example, as base addition salt, sodium salt, metal salt such as potassium salt, calcium salt, magnesium salt and ammonium salt, organic amine salt and the like can be used.

(0014)
The quantity formulated of the aforesaid compound is not restricted in particular in topical agent of this invention, and it can be suitably varied depending on the type of the compound, application purpose and the state of skin, but in general it is 0.005-5.0 wt.% in total quantity of topical agent, preferably 0.05-1.0 wt.%. Moreover, in general, if the quantity formulated of aforesaid compound is less than 0.005 wt.%, there is a situation that the effect is not sufficient, and moreover even when the

quantity formulated exceeds 5.0 wt.%, the enhancement of the potentiation of skin deterioration prevention effect is not observed in some cases, therefore, it is not preferred to be greatly deviated from aforesaid range.

(0015)
A part of the aforesaid compound is well known compound, and for example, it can be readily produced by the method described in Kokai 6-263702 and EP Laid-Open 617020-A1. Moreover, the novel compounds can be readily produced by a person skilled in the art in accordance with processes in Examples of this specification or in aforesaid publication, furthermore by referring to process in accordance with publications such as Kokai 7-17854 and PCT WO 93/6086 in addition to these.

(0016)
In addition to aforesaid to topical agent of this invention, other components used for topical agent such as usual cosmetics, pharmaceutical agent, over the counter drug and the like, can be used. For example, vitamin B2 species such as riboflavin, riboflavin butyrate, flavin adenine dinucleitide and the like, vitamin B6 species such as pyridoxine hydrochloride, pyridoxine dioctanoate and the like, vitamin C species such as L-ascorbic acid, L-ascorbic acid dipalmitate, L-ascorbic acid-2-sodium sulphate and the like, pantothenic acid species such as calcium pantothenate, D-pantotenyl alcohol, pantotenyl ethyl ether, acetyl pantotenyl ethyl ether and the like, vitamin D species such as ergocalciferol, cholecalciferol and the like, nicotinic acid species such as nicotinic acid, nicotinamide, benzyl nicotinate and the like.

(0017)
vitamin E species such as alpha-tocopherol, tocopherol acetate, DL-alpha-tocopherol nicotinate, DL-alpha-tocopherol succinate and the like, vitamin species such as vitamin P, biotin and the like, amino acids and amino acid derivatives such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid and salts thereof, glutamic acid and salts thereof, lysine, arginine, cysteine, cystine, methionine, phenylalanine, tyrosine, histidine, tryptophan, proline, N-acyl acidic amino acid salt such as N-palmitoyl L-aspartic acid diethyl, N-coconut oil fatty acid-L-sodium glutamate and the like, acyl neutral amino acid salt such as coconut oil fatty acid sarcosine triethanolamine, lauroyl methyl-beta-alanine sodium and the like, pyrrolidone carboxylic acid and salts thereof, POE(40) hardened castor oil mono pyroglutamate mono iso stearic acid diester, N-coconut oil fatty acid -L-arginine ethylester -DL-pyrrolidone carboxylic acid salt and the like.

(0018)

Oil such as avocado oil, palm oil, peanut oil, beef tallow, rice bran oil, jojoba oil, evening primrose oil, carnauba low, lanolin, liquid paraffin, squalane, palmitic acid iso stearyl, iso stearyl alcohol, tri-2-ethyl hexanoic acid glycerol and the like, moisturizing agent such as glycerine, sorbitol, polyethyleneglycol, 1,3-butylene glycol, collagen, hyaluronic acid, chondroitin sulfate, dextran sulfate sodium and the like, antioxidant such as sodium erythorbate, para hydroxyanisole and the like, detergent such as stearyl sodium sulfate, cetyl sulfuric acid diethanolamine, cetyltrimethylammonium saccharin, iso stearic acid polyethyleneglycol, arachic acid glyceryl, diglycerol di iso stearate, phospholipid and the like, preservatives such as ethylparaben, butyl para pen and the like.

(0019)
Antiphlogistic such as glycyrrhizin acid derivative, glycyrrhetinic acid derivative, salicylic acid derivative, hinokitiol, zinc oxide, allantoin and the like, beautfiying and whitening agent such as placenta extract, glutathione, Saxifraga extract and the like, extract such as Phellodendron, Coptis, Shikon, peony, sialid, birch, sage, loquat, carrot, aloe, Malva sylvestris, iris, grape, coix, sponge gourd, lily, saffron, Cnidium officinale, ginger, Hypericum erectum, Ononis, rosemary, garlic and the like, activator such as a royal jelly, photo sensitive element, cholesterol derivatives, calf blood extract and the like, blood circulation accelerating agent such as gamma-oryzanol and the like, anti-seborrhoica agent such as sulphur, thianthol and the like, thickener such as carboxy vinyl polymer, carboxymethylcellulose, carboxy hydroxypropylcellulose and the like, flavour, water, alcohol, colour agent such as titanium yellow, casamine, safflower red and the like, or resin powder such as polyethylene, nylon and the like. These can be suitably formulated in accordance with requirements.

(0020)
An effective ingredient of drug useful for prevention and treatment of dermatosis and/or UV absorbent useful for prevention of photo damage and the like may be formulated to the topical agent of this invention. As effective ingredient of such drug, for example, steroidal compound and antibiotics and the like are nominated. As UV absorbent, cinnamic acid series UV absorbent such as para methoxy cinnamic acid-2-ethoxyethyl, para methoxy cinnamic acid isopropyl ester, diisopropyl cinnamate, para methoxy cinnamic acid ethylhexyl, dipara methoxy cinnamic acid mono -2-ethyl hexanoic acid glyceryl, methoxy cinnamic acid octyl and the like, benzoyl methane series UV absorbent such as butyl methoxybenzoyl methane, 4-tert butyl-4'-methoxy-dibenzoyl-methane and the like, benzophenone series UV absorbent such as glyceryl-mono-2-ethyl hexanoyl-di-para methoxybenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxy

benzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sodium sulphonate and the like can be used.

(0021)

Benzoate system UV absorbent such as ortho aminobenzoic acid methyl ester, para dimethylaminobenzoic acid -2-ethylhexyl ester, para dimethylaminobenzoic acid octyl ester and the like, benzoate system UV absorbent such as glyceryl p-amino benzoate, amyl-para-dimethylamino benzoate, ethyl-4-bis hydroxypropyl amino benzoate and the like, other UV absorbent such as 2-ethylhexyl -2-cyano-3,3'-diphenyl acrylate, digalloyl trioleate, salicylic acid-2-ethylhexyl, salicylic acid homo methyl, guaiazulene, urocanic acid and the like can be sued.

(0022)

Topical agent of this invention has an action of preventing the skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging. Accordingly, by applying topical agent of this invention to the daily repair of skin and after sunbathing, deterioration of skin can be prevented, and youthful and healthy state of skin can be maintained. Moreover, agent form of topical agent of this invention is not restricted in particular, and for example agent forms such as solubilisation system such as toner and the like, emulsification system such as milky lotion, cream and the like, or ointment, dispersant, aerosol can be formed. Method of use is not restricted in particular, however, in the case of formulation such as cream agent, a suitable quantity is taken with a finger, and it is applied thinly and thoroughly to face and hand and preferably if it is rubbed into skin by massaging. Below, this invention is further described in concrete terms by Example, however, this invention is not restricted to these Examples.

(0023)

(Examples)

(1) Production of compound.

Example 1: 6-(3,4-diethylphenyl carbamoyl) nicotinic acid.

A liquid mixture of concentrated sulfuric acid 8.1 ml and nitric acid (d = 1.42) 5.16 ml was dropwise-added at 0 degrees to 1,2-diethylbenzene 9.96 g (74.3 mmol) and it was reacted at the same temperature for two hours. The reaction liquor was discharged into ice, and extraction was carried out with ether. The organic layer was washed with water 3 times, with saturated aqueous sodium bicarbonate and with saturated aqueous sodium chloride solution in this order, and the solvent was

eliminated by distillation after dehydration. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent n-hexane / methylene chloride = 19/1), and 3,4-diethyl nitrobenzene 7.8 g was obtained (yield = 58.6 %). Aforesaid 3,4-diethyl nitrobenzene 6 g (36 mmol) and 5 % Pd/c 0.6 g were added to ethanol 100 ml, and catalytic reduction was carried out at normal temperature and normal pressure. The catalyst was eliminated by filtration, thereafter the solvent was eliminated by distillation, and 3,4-diethylamino benzene 4.89 g was obtained (yield: 91.2 %).

(0024)

3-methoxycarbonyl pyridine-2-carboxylic acid 4.62 g (25 mmol) was added to anhydrous benzene 500 ml and thionyl chloride 77 ml and it was reacted for six hours under reflux. The solvent was eliminated by distillation, anhydrous benzene 100 ml was added to the residue, and thionyl chloride was azeotropically-concentrated (three times). Anhydrous benzene 385 ml was added to the residue and dissolution caused, and 3,4-diethylamino benzene 4.5 g (25 mmol) dissolved in dried pyridine 19.2 ml and anhydrous benzene 385 ml was dropwise added to this solution and mixed at room temperature, and it was reacted for three hours under a stream of argon. The reaction liquor was added to iced water 1925 ml, 2 N HCl 77 ml was added and stirred well, and it was extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter it was dried with magnesium sulfate, and it was concentrated and dried to a solid. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent ethyl acetate / n-hexane = 1/3), and crude product 7.57 g was obtained. The obtained product was recrystallised from n-hexane / ethyl acetate, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6.35 g was obtained (yield: 81.4 %).

(0025)

6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6 g (19.2 mmol) was dissolved in methanol 1 l, and 2 N NaOH 200 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl 1.2 litre and extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter dried with magnesium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from ethyl acetate / ethanol, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid 2.9 g was obtained (yield: 50.7 %).

Straw-coloured needle-like crystal, mp 174-176 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 10.57 (s, 1H), 9.16 (d, 1H, J = 2 Hz), 8.50 (dd, 1H, J = 2 Hz, 8 Hz), 8.25 (d, J = 8 Hz), 7.71 (d, 1H, J = 2 Hz), 7.67 (dd, 1H, J = 2 Hz, 8 Hz), 7.14 (d, J = 8 Hz), 2.61 (m, 4H), 1.19 (t, 3H, J = 7.5 Hz), 1.16 (t, 3H, J = 7.5 Hz)
Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.70; H 6.11; N 9.41.

(0026)
Example 2:. 6-(3,4-diethylphenyl carboxamide) nicotinic acid.
nitromethane solution (60 ml) of acetyl chloride 6.44 g (82.0 mmol) and 1,2-diethylbenzene 9.50 g (70.8 mmol) was added dropwise into nitromethane solution (60 ml) of aluminium chloride (AlCl3) 11.4 g (62.2 mmol) and mixed at 0 degrees over a period of one hour. The reaction liquor was stirred at room temperature for two hours, and it was discharged into iced water 150 ml. Ethyl acetate 150 ml was added to this mixture, it was filtered with celite, and the aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layer was recovered, washed successively with water, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution (for each 100 ml), thereafter it was dried with sodium sulfate and the solvent was eliminated by distillation. Vacuum distillation (bp 95 degrees /1.2 mm Hg) was carried out of the residue, and 3,4-diethyl acetophenone 12.0 g was obtained (yield: 96 %).

(0027)
Mixed liquor of 5% NaOCl solution (275 ml) and 25% NaOH solution (33 ml) was added dropwise and mixed to dioxane (160 ml) solution of 3,4-diethyl acetophenone 11.0 g (62 mmol) and it was reacted at 50-60 degrees for two hours. The reaction liquor was cooled and discharged into iced water 1 l, and NaHSO3 was added and thereafter it was adjusted to pH 3 with concentrated hydrochloric acid. This mixture was extracted with ethyl acetate (750 ml, 500 ml). The ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (for each 500 ml), dried with sodium sulfate, and the solvent was eliminated by distillation. Obtained crude product 11.0 g was recrystallised from n-hexane 120 ml, and 3,4-diethyl benzoic acid 10.2 g was obtained (yield: 92 %).

(0028)
Thionyl chloride 28 ml was added to anhydrous benzene (200 ml) solution of 3,4-diethyl benzoic acid 6.5 g (36.5 ml) and it was reacted under reflux for five hours. The reaction liquor was concentrated, thereafter it was substituted twice with anhydrous benzene 50 ml and it was concentrated. Dried THF 25 ml was added to the residue and dissolved, and this solution was added

dropwise and mixed at room temperature to dried THF solution (300 ml) of 6-amino nicotinic acid methyl ester 5.55 g (36.5 ml) and triethylamine 4.61 g (4.56 mmol). The reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated, and ethyl acetate (150 ml) and water (100 ml) were added. The aqueous layer was extracted with ethyl acetate (50 ml x 2), ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (100 ml each), it was dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 300 g, eluent methylene chloride / ethyl acetate = 15/1), and 9.0 g mixture of 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester and diamide body was obtained.

(0029)

This mixture was dissolved in methanol (650 ml), concentrated hydrochloric acid (20 ml) was added and it was reacted at 55 degrees for two hours 30 minutes. The reaction liquor was concentrated, saturated aqueous sodium bicarbonate (400 ml) and methylene chloride (200 ml) were added, and the aqueous layer was extracted with methylene chloride (150 ml, 100 ml). The methylene chloride layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 250 g, eluent benzene / acetone = 30/1), and crude product 5.5 g was obtained. This product was recrystallised from n-hexane (100 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g was obtained (yield: 41 %).

(0030)

6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g (15 mmol) was dissolved in methanol (900 ml) and 2 N NaOH 170 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl (1270 ml) and extracted with ethyl acetate (6 l, 2 l) The organic layer was washed with saturated aqueous sodium chloride solution (2 l), thereafter it was dried with sodium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from chloroform / ethanol = 1/1 (720 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid 2.4 g was obtained (yield: 54 %).

Colourless needle-like crystal, mp 294-295 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.02 (s, 1H), 8.88 (m, 1H), 8.32 (br d, 1H, J = 8 Hz), 8.30 (dd, 1H, J = 2 Hz, 8.8 Hz), 7.88 (d, 1H, J = 2 Hz), 7.82 (dd, 1H, J = 2 Hz, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 2.69 (q, 4H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz) z

Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.25; H 6.08; N 9.10.

(0031)

Example 3: 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid.

A mixture of 3,5-di-tert-butyl benzoic acid (1,800 mg), thionyl chloride (3 ml) and anhydrous benzene (20 ml) was refluxed for six hours. Solvent and excess thionyl chloride were distilled under reduced pressure. The residue was dissolved in anhydrous benzene (15 ml) and a mixture of 6-amino nicotinic acid methyl (500 mg), triethylamine (3 ml), anhydrous benzene (10 ml) was added and it was reacted at room temperature overnight. The reaction liquor was introduced into water, and extraction was carried out with ethyl acetate. The organic layer was washed with water and dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and a mixture (770 mg) of 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester and diacyl body was obtained. This mixture was dissolved in methanol (30 ml), concentrated hydrochloric acid (1 ml) was added and it was refluxed for three hours. The solvent was eliminated by distillation, and methylene chloride and 1 N aqueous sodium bicarbonate were added to the residue. The organic layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester was obtained.

(0032)

6-(3,5-di-tert-butylphenyl carboxamide) methylnicotinate (93 mg) was dissolved by heating to methanol (10 ml). 2 N NaOH (2 ml) was added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was acidified by adding 2 N HCl and thereafter solvent was eliminated by distillation. To the residue were added ethyl acetate and water, the organic layer was separated and was washed with saturated aqueous sodium chloride solution, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was recrystallised from methanol / ethyl acetate, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid was obtained.

Colourless prism crystals, mp >300 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.27 (s, 1H), 8.89 (d, 1H, J = 2.2 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.31 (dd, 1H, J = 2 Hz, 8.5 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.63 (brt, 1H), 1.34 (s, 18H)

Elemental analysis (C21H26N2O3): theoretical value C 71.16; H 7.39; N 7.90, experimental value C 71.19; H 7.66; N 7.88.

(0033)

Example 4: 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid.

5-methoxycarbonyl pyridine-2-carboxylic acid (14 g) was dissolved in benzene (120 ml) and thionyl chloride (85 ml) was added, and it was refluxed for four hours. The solvent was eliminated by distillation, anhydrous benzene was added to the residue, thionyl chloride was eliminated by distillation and acid chloride was obtained. Benzene solution of aforesaid acid chloride (170 ml) was dropwise-added at 20 degrees to pyridine (62 ml) - benzene (100 ml) solution of 3,5-di-tert-butyl aniline (14.9 g) and it was reacted for three hours. The reaction liquor was discharged into iced water (120 ml), 1 N HCl (57 ml) was added and it was extracted twice with ethyl acetate (60 ml). The organic layer was washed successively with 0.5 N HCl (150 ml) and saturated aqueous sodium chloride solution (150 ml x twice), and it was dewatered with anhydrous magnesium sulphate. It was treated with activated charcoal (850 mg), and the solvent was eliminated by distillation, and 26.8 g residue was obtained. It was recrystallised from mixed solvent of n-hexane and ethyl acetate, and ester of 22.5 g was obtained.

(0034)

Aforesaid ester was suspended in methanol (280 ml), and 2 N NaOH (125 ml) was added at 20 degrees or less and it was reacted at room temperature for six hours. 1.5 N HCl (150 ml) was added at 20 degrees or less and precipitated crystals were extracted with ethyl acetate 1.5 l. After washing, ethyl acetate was eliminated by distillation and residue was recrystallised from ethyl acetate - ethanol, and 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid 14.7 g was obtained. mp. 288-289.5 degrees.

(0035)

(2) Production Example of topical agent.

Example 1: Toner.

6-(3,4-diethylphenyl carbamoyl) nicotinic acid	0.05
2-hydroxy -4-methoxybenzo phenone-5-sodium sulphonate	0.1
Acetic acid tocophenol	0.01
Glycerine	4.0
1, 3-butylene glycol	4.0
Ethanol	8.0
Polyoxyethylene (60) hardened castor oil	0.5
Methyl para pen	0.2
Citric acid	0.05
Citric acid soda	0.1

Flavour	0.05
Purified water	balance

(0036)

2-hydroxy-4-methoxybenzo phenone-5-sodium sulphonate, citric acid, citric acid soda, glycerine and 1,3-butylene glycol were dissolved in purified water. Separately, polyoxyethylene (60) hardened castor oil, acetic acid tocophenol, flavour and methyl paraben were dissolved to 6-(3,4-diethylphenyl carbamoyl) nicotinic acid and ethanol, and this solution was added to aforesaid solution and a toner was obtained by filtration.

(0037)

Example 2: cream.

Cetostearyl alcohol	3.5
Squalane	40.0
Beeswax	3.0
Reduction lanolin	5.0
Ethylparaben	0.3
Polyoxyethylene (20) sorbitan mono palmitate	2.0
Stearic acid monoglyceride	2.0
N-stearoyl sodium glutamate	0.5
2-hydroxy -4-methoxybenzo phenone	0.5
Methoxy cinnamic acid octyl	1.0
Retinol acetate	2.0
Evening primrose oil	0.05
Flavour	0.03
6-(3,4-diethylphenyl carboxamide) nicotinic acid	0.1
1,3-butylene glycol	5.0
Polyethyleneglycol 1500	5.0
Purified water	balance

(0038)

Cetostearyl alcohol, squalane, beeswax, reduction lanolin, ethylparaben, polyoxyethylene (20) sorbitan mono palmitate, stearic acid monoglyceride, N-stearoyl sodium glutamate, 2-hydroxy-4-methoxybenzo phenone, methoxycinnamic acid octyl, retinol acetate, evening primrose oil and 6-(3,4-diethylphenyl carboxamide) nicotinic acid were dissolved by heating, and this was added while stirring to purified water together with 1,3-butylene glycol and polyethyleneglycol 1500 which were separately warmed to 75 degrees. It was processed with a homo mixer, the emulsified particles were made fine, thereafter it was rapidly cooled while stirring, and cream was obtained.

(0039)

Example 3: Milky lotion

6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	0.2
Para dimethylaminobenzoic acid -2-ethylhexyl	0.1
Dipara methoxy cinnamic acid mono -2-ethylhexyl	0.2
Stearic acid	1.5
Cetyl alcohol	0.5
Beeswax	2.0
Polyoxyethylene (10) monoolein acid ester	2.0
L-arginine	0.3
L-glutamate Na	0.02
PCA-Na	0.05
Hyaluronate Na	0.01
Propylene glycol	5.0
Glycerine	3.0
Ethanol	3.0
Ethylparaben	0.3
Flavour	0.03
Carboxy vinyl polymer	0.12
Purified water	balance.

(0040)

Flavour was added to ethanol and was dissolved (alcohol phase). On the other hand, L-arginine, L-glutamate Na, PCA-Na, hyaluronate Na, propylene glycol, glycerol, carboxy vinyl polymer were added to purified water and were dissolved by heating, and it was held at 70 degrees (aqueous phase). Furthermore, other components were mixed and dissolved by heating, and it was kept at 70 degrees (oil phase). The oil phase was added to the aqueous phase, preliminary emulsification was carried out, and it was uniformly emulsified with a homo mixer. While stirring this mixture, alcohol phase was added, thereafter it was cooled to 30 degrees while stirring, and amilky lotion was obtained.

(0041)

Example 4: foam mask.

6-(3,5-di-tert-butylphenyl carboxamide)-nicotinic acid	0.02
4-tert butyl-4'-methoxy-dibenzoyl-methane	0.5
Stearic acid	1.0
Behenic acid	1.0
Self emulsification type monostearic acid glycerol	1.5
Monostearic acid polyoxyethylene (5) glycerol	2.5
Batyl alcohol	1.5
Flavour	0.05
Glycerine	5.0
1,3-butylene glycol	5.0
Polyethyleneglycol 1500	3.0
Methylparaben	0.1
Potassium hydroxide	0.15
Purified water	balance
Liquefied petroleum gas	6.0
Dimethylether	2.0.

(0042)

Glycerol, 1,3-butylene glycol, polyethyleneglycol 1500, methylparaben, potassium hydroxide were added to purified water and dissolved by heating at 70 degrees. Other components except for liquefied petroleum gas and dimethylether were dissolved by heating and added to this solution, it was uniformly mixed, and packed into a container. Finally liquefied petroleum gas and dimethylether were added as propellant, and foam mask was obtained.

(0043)

Example 5: ointment.

6-(3,4-diethylphenyl carbamoyl) nicotinic acid	0.1
Para dimethylaminobenzoic acid octyl	4.0
Butyl methoxybenzoyl methane	4.0
Tocopheryl acetate	0.5
Palmitic acid retinol	1.0
Stearyl alcohol	18.0
Japan wax	20.0
Polyoxyethylene (10) monoolein acid ester	0.25
Glycerol monostearic acid ester	0.3
Vaseline	32.0
Purified water	balance.

(0044)

Purified water was kept at 70 degrees (aqueous phase), on the other hand, other components were mixed and dissolved at 70 degrees (oil phase). The oil phase was added to aqueous phase, it was uniformly emulsified with a homo mixer, thereafter it was cooled, and ointment was obtained.

(0045)

(3) Test examples.

Example 1: Action on EGF dependent proliferation of fibroblast.

Proliferation of fibroblast whose proliferation is arrested under low serum condition, is dependent on the growth factor, and the proliferation is promoted with addition of EGF, and when retinoic acid is caused to be co-present further proliferation promotion is performed. Therefore the action on EGF dependent proliferation of fibroblast was examined with respect to the component of topical agent of this invention. PDL12 cells obtained by subculturing human skin fibroblast (HF52) was suspended in 5% FBS-DMEM, inoculated to dish of a diameter of 3.5 cm (47,200 /dish), and cultured at 37 degrees for seven hours, and thereafter the medium was replaced with a culture medium in which DMSO or test compound of prescribed concentration was added to 0.25% FBS-DMEM containing 4 nM EGF, and it was cultured for seven days. The DNA quantity of cells was determined by fluorescence method, and proliferation acceleration ratio was determined.

(0046)

The results are shown in Figure 1. The EGF dependent proliferation was promoted by 40-50 % by the co-presence retinoic acid of 10 [power -6] M concentration. Using the EGF dependent proliferation by this retinoic acid as index, retinoid action of aforesaid compound was examined. As

a result, 6-(3,4-diethylphenyl carbamoyl) nicotinic acid showed proliferation promotion action by 30 % at 10 [power -5] M and by 20 % at 10 [power -6] M, and 6-(3,4-diethylphenyl carboxamide) nicotinic acid showed proliferation promotion action of 20 % at 10 [power -6] M.

(0047)

Example 2:. Flattening action of hairless mouse skin surface configuration (hide furrow) by topical application.

By topical application or internal administration of retinoic acid, skin assumes a reddish tinge and is changed to a glossy and transparent state. Utilising that similar phenomenon can be reproduced with hairless mouse, the action of topical agent of this invention was compared with retinoic acid using a quantitative index corresponding to the change thereof. Retinoic acid acetone solution of 0.05 %, 0.025 % and 0.01 %, and each 1 % acetone solutions of 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid shown in Production Examples, and acetone were respectively applied onto hairless mouse for 30 days (5 times / weeks), and replica of skin surface was cast using silicon series resin on the following day of the final application day, and the various kinds of parameters showing the characteristics of skin surface configuration were determined using image analysis apparatus.

(0048)

By repeated application of retinoic acid, the skin changed concentration dependently to a skin with a reddish tinge and gloss, and retinoid skin-like change observed in human, was produced. Hide crest disappeared on replica with respect to this change, and it was regarded as the change that surface became flattened. It is known that the image analysis parameter KSD (dispersion of luminance distribution in KSD = 3.9 mm x 3.9 mm) is correlated to hide furrow depth (contemporary dermatology system • yearly edition 90B), and this value corresponded well with the action of retinoic acid (Table 1). In each case, the compounds obtained with Production Examples produced retinoic acid-like changes, and although weaker than retinoic acid, KSD change was observed. In histological examination, the inflammatory changes (cell infiltration within dermis and epidermis, intercellular • intracellular edema, vasodilation and the like) found in retinoic acid were not observed in any of the test compounds. The clearest change was acanthosis (Table 2)

(0049)

(Table 1)

	KSD change (%)

Acetone	89.7%
0.01 % retinoic acid	79.2 %
0.025 % retinoic acid	73.4 %
0.05 % retinoic acid	33.6 %
1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	84.5 %
1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid	83.7 %
1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	78.3 %
1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	76.9 %

(0050)

(Table 2)

	Acanthosis (μm)
Acetone	18 μm
0.01 % retinoic acid	48 μm
1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	22μm
1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid	21 μm
1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	32 μm
1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	35 μm

(0051)

Example 3: Action with respect to rhinomouse skin.

On the epidermis of the rhinomouse, egg shaped cysts (utricle) that contain keratin derived from trichocyst are present. This egg shaped cyst is known to shrink due to retinoic acid administration (doe example, Ashton, R. E. et al, J. Invest. Dermatol., 82, pp. 632-635, 1984 and the like). The aforesaid action was examined with respect to the compounds shown in Production Examples. Test compound solution of prescribed concentration and carrier 0.1 ml were applied onto dorsal skin of 8 week old female rhinomouse in a frequency of once or twice per day, 5 days per week over two week period. For the purpose of histological evaluation, the dorsal skin was excised, the epidermis was separated from the dermis using 0.5 % acetic acid, and epidermis sheet for light microscopy observation was produced. The image data obtained via CCD camera was analysed, and the area of egg shaped cysts was determined. The results are shown in Table 3. The retinoic acid showed strong skin flare, but skin flare was not observed at all with the compounds shown in Production Examples.

(0052)

(Table 3)

	Decrease of egg shaped cysts area (vs carrier, %)					
	0.00001 %	0.0001 %	0.001%	0.01 %	0.1 %	1 %
Retinoic acid	77	59	15			

1% 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	90	87	60
1% 6-(3,4-diethylphenyl carboxamide) nicotinic acid	95	89	50
1% 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	80	62	40
1% 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	81	58	30

(0053)

Example 4: Metabolic Test.

One of the reason why the retinoic acid shows toxicity in human, is that the retinoic acid is hard to be metabolised. Therefore, the metabolism of two types of the compounds shown in Production Examples was evaluated by the following method. The test substance which was dissolved in ethanol was added to a buffer containing a specified quantity of rat liver homogenate (25 % homogenate in which rat liver 25 g from which blood was eliminated by irrigation with 0.15 M KCl solution was homogenised with 75 ml phosphate-buffered liquid of pH 7) (final concentration 10 [power -4] M), and the residual quantity of test substance was determined with time by HPLC. The results are shown in Table 4. From the obtained results, it was indicated that the compounds of this invention were readily metabolised in vivo.

(0054)

(Table 4)

Metabolism in rate liver homogenate

Compound	Residual quantity after 10 min. (%)	Residual quantity after 60 min. (%)
6-(3,4-diethylphenyl carbamoyl) nicotinic acid	65	5.0
6-(3,4-diethylphenyl carboxamide) nicotinic acid	55	3.0

*t = 0 as 100 %

(0055)

Example 5: stability test

Ethanol solution of each compound 300 ppm obtained in Production Examples was irradiated with xenon light for 30 hours, or was stored at 50 degrees two months, thereafter the residual quantity was determined by HPLC. As a result, all the compound was confirmed to be remaining by 95 % or more. On the other hand, retinoic acid was rapidly decomposed under the same conditions.

(0056)

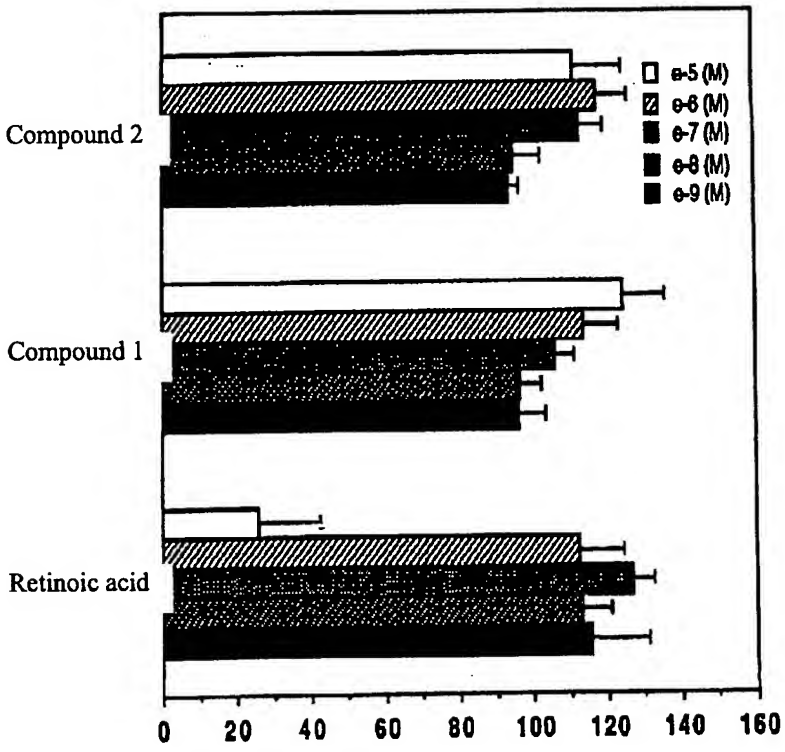
(Advantages Afforded by this Invention)

The compound of aforesaid formula which is a component of topical agent of this invention has excellent skin deterioration prevention action, and, in addition, it is stable, percutaneous absorption is small, and safety is high. Moreover, even when absorbed in body, it is readily metabolised, therefore, there is a characteristic that side effect due to retinoid action is not caused.

(Brief Description of the Figures)

(Figure 1) It is a figure showing the action of representative compounds contained in topical agent of this invention on the EGF dependent proliferation of fibroblast. Compound 1 in figure shows 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, and compound 2 shows 6-(3,4-diethylphenyl carboxamide) nicotinic acid.

(Figure 1)



Rising Sun Communications Ltd. Terms and Conditions

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.